US EPA ARCHIVE DOCUMENT

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OCT 17 1989

007548

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Metiram: Response to Evaluations of a Chronic Toxicity/Oncogenicity Study in Rats and an Oncogenicity Study in Mice.

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Special Review and Registration Division (H7508C)

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EPA ID No.: 014601-9
MRID No.: 41163101; 41163102
Project No.: 9-1911
Caswell No.: 41A
Registrant: BASF Corp.

Requested Action

Review submitted data and provide comments.

I. Chronic Toxicity/Oncogenicity Study in Rats (BSF/199/80391; 5/7/81)

This study, in which Metiram was administered in the diet of Charles River CD rats at levels of 5, 20, 80 or 320 ppm for 111 weeks (females) to 119 weeks (males), was originally reviewed by Dynamac Corp. (DER dated August 14, 1986) and further reviewed by TB (Ghali, HED, to Rossi, RD, December 12, 1986). The reviewers noted the following deficiencies:

1) The histopathology summary tables showed only the number of animals examined, not the number of tissues.

2) The rats could possibly have tolerated a slightly higher dose since the only toxic effect noted was an increased incidence of minimal to moderate muscular atrophy of the thighs in male and female rats receiving the highest dietary level. The reviewer (Dynamac) also noted that statistical analysis of atrophic changes of skeletal muscle could not be performed until deficiency no. 1 is addressed.

TB Response

Deficiency No. 2 was previously addressed by TB (Swentzel, HED, to Rossi/Grable, RD, June 15, 1989). TB concluded that the doses selected for this study were appropriate, based on adverse effects observed in range-finding and subchronic studies. However, it was indicated that the registrant did not discuss the examination of the sciatic nerve relative to the noted effects in skeletal muscle and that any associated information should be submitted.

The current submission includes revised histopathology tables which show the number of tissues examined for each organ in each group. Based on these data, the following incidence of skeletal muscle atrophy was determined:

Skeletal Muscle Atrophy Incidence (No./50)

Dietary levels (ppm)	0	5	20	80	320
Males					
Minimal	11	16	15	14	22*
Moderate	6	7	6	5	16*
Marked	2	0	0	0	0
Total	19	23	21	19	38**
Females					
Minimal	9	5	5	5	21**
Moderate	2	0	1	2	18**
Marked	0	0	0	0	0
Total	11	5	6	7	39**

* $p < 0.05$; ** $p < 0.01$, Fisher's Exact

These data show that the increased incidence of skeletal muscle atrophy observed in high-dose males and females is statistically significant.

II. Oncogenicity Study in Mice (BSF 198/78265; 6/5/79)

The primary evaluation of this study, in which Metiram (fortified with 2 % ETU)

was administered in the diet to male and female CFLP mice for 96 weeks at levels of 100, 300 or 1000 ppm, was performed by TB (Ghali, HED, to Jacoby, RD, February 16, 1981). In addition to other noted deficiencies (Swentzel, HED, to Rossi/Grable, RD, June 15, 1989), it was indicated that the mice could have tolerated a higher dosage level since no treatment-related effects were observed.

The current submission includes a study entitled Preliminary Assessment of Metiram Toxicity to Mice in Dietary Administration for 4 Weeks (Document no. 76/0014, completed in June 1976 by Huntingdon Research Centre). Evidently, this study was submitted to support the selection of doses for the oncogenicity study. Male and female CFLP mice were administered untreated diet or Metiram at dietary levels of 100, 300, 1000 or 3000 ppm for the duration of the study. The only consistent changes observed in treated mice were inhibited body weight gain (Appended page 1) in females at the 3000 ppm level, which did not correlate with food conversion ratios, and increased absolute and relative liver weights in males and females at the 1000 and 3000 ppm levels (Appended pages 2 through 5). Gross examination did not reveal any abnormalities in the liver of treated animals, histopathologic examinations were not performed. Considering the minimal toxicity that was observed in this study, it does not appear that it supports the dosages selected for the oncogenicity study. It is the Agency's position that the highest dose to be tested in the oncogenicity study should be selected below a level which resulted in sigfificant life-threatening toxicity in a subchronic study. There is no convincing evidence in this study that 3000 ppm was a life-threatening level.

Conclusions

The registrant has submitted the histopathologic data, which show the number of each tissue examined in addition to the number of animals examined in each group, for the chronic toxicity/oncogenicity study with Metiram in rats. This allowed a pairwise comparison of the incidence of skeletal muscle atrophy between control and high-dose animals, which showed that the increased incidences observed in the latter group were statistically significant ($p < 0.05$) in both males and females. The core-classification of the oncogenicity segment of this study should be upgraded to core-minimum. The core-classification for chronic toxicity can not be upgraded because a NOEL for systemic toxicity could not be established.

Based on the minimal toxicity observed, the data in the 4-week dietary study with Metiram in mice did not support the dose selection for the oncogenicity study. Therefore, it remains TB's opinion that the mice in the oncogenicity study could have tolerated a higher dietary level of Metiram. The NOEL in this study was 301 ppm and the LEL was 1000 ppm based on increased liver weights.

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